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08/711,961	09/06/96	BRANSTROM	

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DATE MAILED: 10/10/97

Please find below a communication from the EXAMINER in charge of this application

Commissioner of Patents

See the attached.

Office Action Summary	Application No. 08/711,961	Applicant(s) Branstrom et al.
	Examiner J. Railey	Group Art Unit 1805

☒ Responsive to communication(s) filed on *29 Jul 1997*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-44* is/are pending in the application.

Of the above, claim(s) *1-27 and 34-43* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *28-33 and 44* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

The Examiner in charge of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1805, Examiner Railey.

Claims 1-27 and 34-43 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 6.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 28 and 31-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Curtiss, III [U.S. Patent 5,672,345].

Applicant claims methods of delivering DNA to a cell by administering to that cell an attenuated *Shigella*. The *Shigella* is attenuated by having an attenuation factor which will result in the lysis of the *Shigella* after entry into the cell. The methods claimed also are drawn to the cell being of a mucosal epithelium, intestinal mucosal epithelium or to *Shigella* which is further inactivated.

Curtiss, III teaches modification of the *asd* gene in *Shigella*. See column 17, beginning at line 19, in which *Shigella* species are embraced by the invention. The microbe will lyse in

the absence of DAP. See column 16, line 49. Administration of the cell to an animal will result in lysis of the bacteria and delivery of the nucleic acid to the cell. See column 20, line 60. The bacteria can be used to deliver heterologous or homologous antigens to lymphoid tissue such as the GALT. The bacteria can be rendered avirulent. See column 20, line 66 and column 22, line 7.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29, 30 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curtiss, III [U.S. Patent 5,672,345].

Applicant claims embodiments in which *Shigella flexneri* or a specific mutant of *Shigella*

flexneri is used in the methods. Further, claim 44 is drawn to delivery of "functional nucleic acids". The generation of specific mutants of *Shigella flexneri* would have been obvious as a species of bacteria disclosed by Curtiss, III, absent evidence to the contrary. The delivery of "functional nucleic acids" would have been obvious, given that the term is ambiguous. See the grounds of rejection below under 35 U.S.C. 112, second paragraph. In addition, applicant's response, paper No. 8, received 29 July 1997 notes at page 7:

> The term functional is thus intended to mean that the nucleic acid can perform the normal functions expected of nucleic acids which result in the production of expected end products.

Given this definition, applicant's invention would have been obvious given the teachings of the prior art.

Applicant may obviate the rejection based upon the prior art by including limitations in which the DNA which is delivered to the (mammalian) cell is capable of being expressed within that cell. Curtiss, III does not suggest in any embodiments that the modified bacteria administered to the cell will transfer any DNA capable of being expressed by the mammalian cell which receives it. Curtiss, III is concerned with delivery of modified bacteria which has already expressed the antigens as protein components. Lysis of the bacteria once administered will release these protein components, which then serve as immunogens.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode

contemplated by the inventor of carrying out his invention.

Claims 28-33 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for attenuation of *Shigella* strains by inactivation of the gene encoding aspartate β-semialdehyde synthetase (*asd*), does not reasonably provide enablement for nutation of other attenuation factors which will result in lysis of *Shigella*, or other bacteria as broadly claimed. In addition, the specification does not provide for strains of bacteria other than *Shigella* for delivery of DNA to a "cell". Finally, regarding the type of "cell" which receives the DNA, applicant has only taught mammalian cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is noted that applicant's response of 29 July 1997, paper No. 8, has amended claim 44 to require that the bacteria have an "attenuating factor which will result in the lysis of the bacteria after entry into said cell." Claims 28-33 have been amended to require that the *Shigella* have an "attenuating factor which will result in the lysis of the Shigella after entry into said cell." The grounds of rejection which follow are based upon applicant's newly amended claims.

The specification teaches how to make mutations in the *asd* gene within strains of *Shigella*. The mutations inactivate the gene encoding aspartate β-semialdehyde synthetase, causing the strain to be dependent upon exogenous diaminopimelate (DAP) supplied in the growth culture. *Shigella* normally will invade mammalian cells, disrupt the endocytic vacuole and escape, thus allowing replication and spread of the bacterium to adjacent mammalian cells. See

applicant's response, paper No. 8, received 29 July 1997, at pages 2-4. Applicant's *asd* mutants are able to invade mammalian host cells, are able to disrupt the endocytic vesicle, yet are not able to replicate in the host mammalian cell. *Shigella* die by lysis, and empty their nucleic acid into the cytoplasm of the host mammalian cell. If the *Shigella* harbors a mammalian DNA expression plasmid, the plasmid is delivered to the host mammalian cell cytoplasm and expressed. Applicant broadly claims methods in which the *Shigella* has any mutation which results in the lysis of the *Shigella* after entry into the "cell" (presumably mammalian host cell). Applicant also broadly claims methods in which any bacteria is used like the *Shigella* example. The specification fails to teach how to make and use mutations other than the *asd* mutation. Further, the specification fails to teach how to make and use bacteria other than *Shigella* as broadly claimed.

The first issue is in regard to the generation of mutations, other than in the *asd* gene, which would result in lysis of the bacteria following bacterial entry into the host mammalian cell. The specification at page 10 specifically teaches a mutant *asd* gene, SEQ ID NO:2, and instructs the skilled artisan how to generate *Shigella* strain 15D. The specification teaches selection methods for detecting mutants in the *asd* gene and culturing methods for maintaining such strains. The specification at page 9, lines 19-23 asserts that other genes, such as "*thy A*, genes for LPS production, *htrA* and *htrB*, and *dut*" are functionally equivalent to the *asd* gene. However, the specification fails to teach the sequence of these genes, proper mutations which inactivate them,

selection methods for obtaining such mutants and culture techniques for maintaining mutant isolates. The skilled artisan is left with no guidance as to these methods and techniques for generating equivalents to mutations in the *asd* gene. As these other gene sequences are not taught and the skilled artisan would be unable to make and use proper mutations which would result in a phenotype equivalent to *asd* mutants, it would require undue experimentation to practice the invention for its scope.

The second issue is in regard to the use of bacteria species other than *Shigella* in the invention as broadly claimed. Applicant's specification at page 35 notes that this is a "novel method for delivering functional DNA inside cells." The specification asserts that other bacteria that can break out of the phagocytic vacuole into the cytoplasm, such as *Listeria*, could be used in the methods as claimed. Applicant even admits that another enteric, *Salmonella typhimurium*, is an example of a bacteria which is not efficient at delivery of DNA. (In fact, as noted in Sizemore et al. [Vaccine **15(8)**:804-807 (1997)], at page 807, *asd* mutants of *Salmonella typhimurium* will need to be "further engineered" before it will be efficient as a DNA delivery vehicle. How this further engineering is to occur is not specified.) At most, applicant's claims should be limited to species of bacteria capable of disrupting the phagocytic vacuole in the mammalian cell. Even then, as noted at page 35, line 15, of the specification other bacterial vector DNA delivery systems "will need to strike a balance between cell invasion and its subsequent reactogenicity and efficiency of delivery." The specification fails to teach how to

make and use such strains of bacteria having these properties, other than for *Shigella*. For essentially the same reasons as set forth in the preceding paragraph regarding the first issue, the specification fails to teach how to make and use other genes in other bacterial species. No gene sequences are taught and no methods of screening and selecting mutants in other bacterial species are shown. Each species of bacteria is unique in its phenotypic properties and as applicant has "no formal proof that release from the phagocytic vacuole into the cell cytoplasm by the bacteria is essential for DNA delivery," extrapolation of the results from *Shigella* to other species of bacteria is inherently unpredictable. As broadly claimed, it would require undue experimentation to develop attenuated mutants of other species of bacteria characterized by lysis once inside the host mammalian cell, while having the ability to deliver plasmid DNA capable of being expressed within that mammalian cell.

The last issue is in regard to the type of "cell" which receives the DNA. Applicant has amended the claims to require that the bacteria or *Shigella* which enters the "cell" must be capable of lysis once inside the "cell." The specification teaches only the use of mammalian cells for uptake of *Shigella* and delivery of the DNA. *Shigella* (or broadly claimed bacteria) is not shown capable of having this specific property with any other types of eukaryotic "cells." Particularly, the *Shigella* mutants must be able to attach to the cells and be taken up in a phagocytic vacuole, prior to disruption of, and release from, that vacuole. No other "cells" are shown to have the proper vacuole environment which permits uptake of the *Shigella*, disruption

of the vacuole, lysis of the bacteria and release of the DNA. This is an important point if the DNA is to be expressed efficiently by the mammalian host cell.

Regarding the rejection of claim 30 under 35 U.S.C. 112, first paragraph, for insufficient description of the *Shigella flexneri* clone 15D, applicant's response at pages 6-7 notes that the clone has been deposited at the ATCC under assession no. 55710. Applicant states that the required assurances as to the continued availability of the microorganisms will be provided in due course. Until applicant completes the requirements as set forth in the previous office action, paper No. 7, mailed 29 April 1997, this rejection is maintained. Applicant is reminded to review and amend the specification to include this depository information if necessary.

Claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is maintained for reasons as set forth in the previous office action. The term "functional nucleic acids" is not defined in the specification. Applicant's response directs the examiner to page 1, lines 18-19 for support. However, the specification at this section does not define the term. Rather, the specification states:

> The nucleic acids delivered to the cell in this way can direct the eukaryotic cell to produce antigens or other functional molecules.

Other than defining the nucleic acids as expressing "antigens," this is a circular definition which

defines "functional nucleic acids" as producing "functional molecules." Consequently the term is still vague and indefinite insofar as the phrase "other functional molecules" is not elaborated upon in the specification.

The following allowable claim is suggested:

A method for delivering DNA capable of being expressed in a mammalian cell, said method comprising:

(i) introducing said DNA into an attenuated strain of *Shigella* which is unable to synthesize active aspartate β-semialdehyde dehydrogenase; and

(ii) administering the *Shigella* of (i) to a mammalian cell such that the *Shigella*, after uptake by the mammalian cell, will lyse, thereby delivering to the mammalian cell the DNA capable of being expressed therein.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Art Unit 1805 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number for Art Unit 1805 is (703) 308-4242 or 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. F. Railey, whose telephone number is (703) 308-0281. The examiner can normally be reached on Monday-Thursday, and alternate Fridays, from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax phone number for informal transmissions to the examiner is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

9 October 1997

JOHNNY F. RAILEY II, PH.D.
PRIMARY EXAMINER
GROUP 1800